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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,163	08/01/2003	Nicholas M. Dean	ISPH-0755	5447

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,163	DEAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 01 August 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/1/2003.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-17 are currently pending and are currently under examination.

Applicant filed a sequence list disclosing SEQ ID NO:47 as a nucleic acid and the claims are specifically to SEQ ID NO:47 as a nucleic acid. It is noted that the specification as filed does not disclose a SEQ ID NO for the asserted polypeptide sequence encoded by SEQ ID NO:47.

Information Disclosure Statement

The information disclosure statement filed on 08/01/2003 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because of the following reasons:

The non patent literature document AC on page 1 of has not been considered because the document is not in the instant application or the parent application and therefore appears to not have been filed.

The foreign patent document AB on page 3 of 3 has not been considered because the document is not in the instant application or the parent application and therefore appears to not have been filed.

Therefore the documents, per above, contained in the information disclosure statement filed on 08/01/2003 have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 recite "TGF-a2" as being SEQ ID NO:47. It is unclear what is meant by "a2" because the specification discloses SEQ ID NO:47 as murine TGF-**β2**. It appears this is a typographical error.

Therefore, for the purposes of compact prosecution "TGF-a2" is being interpreted as "TGF-β2", since the specification clearly indicates SEQ ID NO:47 as TGF-β2 and SEQ ID NO:47 is specifically claimed as TGF-β2.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 recite "a nucleic acid molecule encoding TGF-a2 (SEQ ID NO:47)". It is unclear whether SEQ ID NO:47 is a polypeptide or a polynucleotide. The specification discloses SEQ ID NO:47 as a polynucleotide (see page 61, Example 1) and the Sequence List as filed discloses SEQ ID NO:47 as a polynucleotide (see page 16, line 21). It is suggested the claim state, "a nucleic acid molecule (SEQ ID NO:47) encoding TGF-β2".

Claims 13-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting transforming growth factor beta 2 (TGF-β2) in murine cells in vitro and enabling for a method of treating conjunctival scarring in a rabbit following glaucoma filtration surgery by administration of an antisense targeted to TGF-β2, does not reasonably provide enablement for a method of inhibiting TGF-β2 in any cell or tissue and a method for treating conjunctival scarring in any animal by administration of an antisense targeted to TGF-β2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to a method of inhibiting expression of TGF-β2 in cells or tissues by administration of an antisense targeted to TGF-β2. Further, the claims are drawn to a method of treating an animal having a disease or condition associated with TGF-β2 by administration of an antisense targeted to TGF-β2. The claims further recite the disease or condition is inflammation, fibrosis or a fibrotic disease and further wherein the fibrotic disease is fibrotic scarring, peritoneal adhesions, lung fibrosis or conjunctival scarring.

The specification as filed discloses a method of inhibition of TGF-β2 in murine cells, in vitro, by administration of an antisense targeted to a gene encoding TGF-β2 (SEQ ID NO:47). The specification further discloses a method of decreasing conjunctival scarring in a rabbit following glaucoma filtration surgery by administration of an antisense targeted to a gene encoding TGF-β2 (SEQ ID NO:47). The specification as filed does not disclose that because of administration of an antisense compound targeted to TGF-β2, TGF-β2 is inhibited in any cells or tissue and further conditions or diseases associated with TGF-β2 are treated in any animal.

There is no guidance in the specification as filed that teaches how to target the claimed antisense compound to human cells or tissues, inhibit the expression of TGF-β2 *in vivo*, and further provide treatment for inflammation or fibrosis. Although the specification discloses inhibition of murine TGF-β2 *in vitro* by administration of antisense compound and discloses decreased conjunctival scarring in rabbit after administration of an antisense targeted to a gene expressing TGF-β2, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 13-17 encompass a method of inhibition of TGF-β2 in murine cells, in vitro, by administration of an antisense targeted to a gene encoding TGF-β2 (see Example 21) and further encompass a method of decreasing conjunctival scarring in a rabbit following glaucoma filtration surgery by administration of an antisense targeted to a gene encoding TGF-β2 (see Example 24), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds. Branch stresses that "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense

molecules must be found empirically by screening a large number of candidates for their ability to act inside cells" (TIB 23: 45-50 1998). Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2).

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

As outlined above, it is well known that there is a high level of unpredictability in the antisense art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely inhibition of TGF-β2 in any cell or

tissue and further treatment of a condition or disease associated with TGF-β2 by administration of an antisense compound targeted to a gene encoding TGF-β2.

While one skilled in the art may be able to find an antisense oligonucleotide targeted to a gene encoding TGF-β2 and demonstrate inhibition of TGF-β2, *in vitro,* by using the antisense oligonucleotide, the specification as filed does not teach how to administer any antisense oligonucleotide to any cells or tissues of any animal and further to treat any disease or condition associated with TGF-β2 by administration of the antisense compound, as claimed.

Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) supports the difficulties of extrapolating from in vitro experiments and states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

Further, treatment of conjunctival scarring by administration of antisense oligonucleotide is not predictive of treatment of conjunctival scarring in any other mammal. Cordeiro *et al.* (Gene Therapy 2003, Vol. 10: 59-71) states "...the rabbit model...a involves conjuctival scarring response that is complicated by the presense of a fluid called aqueous humour and dynamically changing conditions. The TGF-β antisense ODN would be expected to have maximal effects on local cellular production of TGF-β at the filtration wound site and not in aquous which is know to contain high concentrations of TGF-β2 protein in association with glaucoma and intraocular fibrosis" (see page 63, column 2).

Thus, the rabbit model of conjunctival scarring does not predict inhibition TGF-β2 in any cell or tissue by administration of an antisense molecule targeted to a gene encoding TGF-β2 and further does not predict treatment of conjunctival scarring by administration of an antisense molecule targeted to a gene encoding TGF-β2 in any mammal.

In view of the unpredictability in the art of antisense-based therapy, as outlined above, and the unpredictability of applicant's animal model of conjunctival scarring, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention in any animal without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by Petkovich *et al.* (U.S. Patent No: 6,306,624).

The instant claims are drawn to a compound 8 to 50 nucleobases in length targeted to the 3' untranslated region of a nucleic acid molecule (SEQ ID NO:47) encoding TGF-β2 wherein said compound modulates the expression of TGF-β2.

Petkovich *et al.* teach a compound, 17 nucleobases in length (SEQ ID NO:21) targeted to the 3' untranslated region of a nucleic acid molecule encoding TGF-β2 (see specification, columns 61 and 63). The nucleic acid sequence taught by Petkovich *et al.* meets the structural limitation of claims 1-2 of the instant application and, absent evidence to the contrary, would modulate expression of TGF-β2.

Thus, Petkovich *et al.* anticipates claims 1-2 of the instant application.

Claims 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by Ishiwata *et al.* (U.S. Patent No: 6,828,428).

The instant claims are drawn to a compound 8 to 50 nucleobases in length targeted to the 3' untranslated region of a nucleic acid molecule (SEQ ID NO:47) encoding TGF-β2 wherein said compound modulates the expression of TGF-β2.

Ishiwata *et al.* teach a compound, 17 nucleobases in length (SEQ ID NO:105) targeted to the 3' untranslated region of a nucleic acid molecule encoding TGF-β2 (see specification, column 95, line 23). The nucleic acid sequence taught by Ishiwata *et al.* meets the structural limitation of claims 1-2 of the instant application and, absent evidence to the contrary, would modulate expression of TGF-β2.

Thus, Ishiwata *et al.* anticipates claims 1-2 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petkovich *et al.* (U.S. Patent NO: 6,306,624), in view of Bennett *et al.* (U.S. Patent NO: 6,077,833).

The invention of the above claims is drawn to antisense compounds, 8 to 50 nucleobases in length, that target the 3' untranslated region of a nucleic acid sequence (SEQ ID NO: 47) encoding TGF-β2, and further drawn to said compounds comprising internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) or chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents or colloidal dispersion systems thereof, and methods of use.

Petkovich *et al.* teach an antisense compound targeted to the 3' untranslated region of a nucleic acid sequence (SEQ ID NO: 47) encoding TGF-β2. Petkovich *et al.* do not teach antisense sequences comprising linkage, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents or delivery systems thereof.

Bennett *et al.* teach targeting 3'-untranslated regions of a desired target in column 7. Column 10 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly

preferred. Columns 6-7 teach that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, among others. Columns 8-9 teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. Bennett *et al.* also teach one of ordinary skill to modify nucleobases in antisense oligonucleotides, including the teaching of 5-methylcytosine (col. 9), and also to use chimeric antisense oligonucleotides (col. 10). Bennett *et al.* teach that the above modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Column13 teach the antisense oligonucleotide can be in a pharmaceutically acceptable carrier and column 14 teach dispersion systems.

It would have been obvious to one of ordinary skill in the art to incorporate the modifications as taught by Bennett *et al,* into the antisense sequences targeted to a nucleic acid molecule encoding TGF-β2 as taught by Petkovich *et al.*

One would have been motivated to modify such antisense compounds because Bennett *et al.* teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation.

Finally, one would have a reasonable expectation of success given that Bennett *et al.* teach modified antisense compounds targeted to distinct regions of a target gene decrease expression of the target gene (see Examples 3, 4 and 7).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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